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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/633,742	08/04/2003	Kevin Gene Peters	9045M	1253

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EXAMINER	
NASHED, NASHAAT T	
ART UNIT	**PAPER NUMBER**
1656	

DATE MAILED: 05/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/633,742	PETERS ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *15-17* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/18/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election with traverse of Group I, claims 1-14, in the reply filed on March 6, 2006 is acknowledged. The traversal is on the ground(s) that inventions I-IV are closely interrelated and in order to preserve unity of invention, all claims should be prosecuted together in the same application. This is not found persuasive because the instant application is a non-provisional U. S. application not filed under 35 USC 371. Thus, the rules of unity of invention do not apply in this case. The applicants have failed to show that the inventions are not distinct, and/or a search burden does not exist in order to examine inventions I-IV. Inventions II-IV could not be classified because they are too broad to have any classification as they are directed to method of testing and using modulator of angiogenesis, and a composition of said modulator. Thus, inventions I-IV are distinct from one another, and examining them together would constitute a search burden on the examiner. Applicants' traversal of the election of species fail short of the requirement for traversing the election of species because they have not submitted any evidence or argue that the different species of the invention are obvious over one another.

The requirement is still deemed proper and is therefore made FINAL.

The use of the trademarks "IIPOFECTAMIN-PLUS", "GENETICIN", "CATCHER", "TAQMAN", "LIPOFECTIN", and "OTIMEM-I" have been noted in this application, see for example page 25, lines 17 and 19, and page 28, lines 10, 11, and 18. They should be all capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s). In particular, 37 CFR 1.821, which states:

> (d) Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Thus, each time the HPTPbeta catalytic domain, and VEGFR2 and Tie-2 kinase domain appear in the specification or in the claims, it should be accompanied by SEQ ID NO: (see for example page 23, line 1, and 22, and page 25, line 16.

> The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) The phrase "treating an angiogenesis mediated disorder" in claim 1 renders the claims indefinite because resulting claims do not define the metes and bound of the claimed invention. It is noted that the specification attempts to define the phrase at page 9, starting at line 14, but the definition is indefinite because it does not define the diseases encompass by the phrase. For examination purposes only, the phrase is taken to mean any disease involving blood vessels such as cancer, vascular disease including coronary artery disease and stroke, and diabetes related vascularization.

(b) The phrases HPTPbeta and VEGFR2 in claims 1-14, and Tie-2 in claims 8-12 render the claims indefinite because resulting claims do not define the metes and bound of the claimed invention. Abbreviations and acronyms must be defined at least once in the claims.

(c) The phrases "HPTPbeta activity" and "VEGFR2 activity" in claims 1 and 8, and Tie-2 activity render the claims indefinite because resulting claims do not define the metes and bound of the claimed invention. The "HPTPbeta activity is presumed to be any protein tyrosine phosphatase activity, and VEGFR2 and Tie-2 activity are any protein tyrosine activity.

(d) The phrase "hydrolysis of phospho-ester bond of one or more natural or artificial phosphate containing compound" in claims 6 and 13 renders the claim indefinite because resulting claims do not define the metes and bound of the claimed invention. First, the phrase phospho-ester referes to any phosphate esters including cAMP, RNA, and DNA, but HPTPbeta is disclose to catalyze the hydrolysis of phosphate monoesters such as phosphoserine in a protein. Second, one of ordinary skill in the art can't distinguish between a natural phosphate ester and an artificial one.

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-11, 13, and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way

as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4, 6-11, 13, and 14 are directed to a method of identifying qan agent that is useful in treating any angiogenesis related disorder using any human protein tyrosine phosphatase beta, and VEGFR2 and Tie-2 protein kinase from any biological source including those having 80% 0r 90% homology to SEQ ID NO: 2, 6 and 8. The specification, however, only provides: (a) HPTPbeta of SEQ ID NO: 2 (wild-type) fragments thereof having the amino acid sequences of SEQ ID NO: 9, 15, and 16; wild-type VEGFR2 of SEQ ID NO: 6 and fragment thereof of SEQ ID NO: 11; and Wilod type Tie-2 and fragment thereof of SEQ ID NO: 13. There are no disclosures of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these HPTPbata, VEGFR2 and Tie-2 by any identifying structural characteristics or properties other than the amino acid sequences disclosed in claim 5, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 1-4, 6-11, 13, and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are broader than the enablement provided by the disclosure with regard to all possible proteins which can be described as HPTPbeta, VEGFR2 or Tie-2 or having 80% or 90% homology to any of the amino acid sequences of SEQ ID NO: 2, 6, 8, 9, 11, 13, 15, and 16. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses a method of identifying an agent useful for treating any angiogenesis related disease by contacting any proteins similar to HPTPbeta, and VEGFR2 with or without Tie-2 in one way or another to the protein having SEQ ID NO: 2, 6, 8, 9, 11, 13, 15, and 16, or having 80% or 90% homology to any of the amino acid sequences of SEQ ID NO: 2, 6, 8, 9, 11, 13, 15, and 16. The specification provides guidance and examples in the form of an assay to obtain the proteins SEQ ID NO: 2, 6, 8, 9, 11, 13, 15, and 16, and assays useful for identifying modulator for the activities of said proteins (see exampled 1-10). While molecular biological techniques and genetic manipulation to make any desired protein

are known in the prior art and the skill of the artisan are well developed, knowledge regarding all human proteins having similar activities to SEQ ID NO: 2, 6, and 8, their variants, and their biological functions is lacking. Thus, searching for all possible human proteins having some similarities to any of SEQ ID NO: 2, 6 and 8 is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation to identify a new gene involved in angiogenesis having simal structure or functions to those of SEQ ID NO: 2, 6, and 8 is enormous. Since routine experimentation in the art does not include screening vast numbers of human gene or cDNA libraries or man-made libraries to identify variants and homologs of SEQ ID NO: 2, 6, and 8, identifying their biological function, and their role in angiogenesis, where the expectation of obtaining the desired protein and identifying its biological function is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the amino acid sequences and the corresponding nucleic acid sequences of horologes and variants, and their biological functions as the relate to angiogenesis. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 6-9, 13, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang *et al.* (IDS reference: J. Biol. Chem. 1999, 274, 38183-38188), in view of U. S. patent 6,342,219 ('219, Thorp *et al.*).

Huang *et al.* teach a human protein tyrosine phosphatase and named it (HCPTPA), which interacts and negatively regulates VEGFR2 and appears to have the same function of HPTPbeta, see the abstract and the first paragraph of the discussion at page 38186, right column. Also, they teach that the over expression of HCPTPA in a VEGF-dependent model of angiogenesis, the rat aortic ring assay, blocked the formation of vascular sprout; see the paragraph bridging pages 38186 and 38187. In addition, they teach that HCPTPA binds to Tie2, but does not bind to Tie1 and VEGFR1, see page 38188, left column, second paragraph. Huang *et al.* does not teach, however, a method of identifying an agent useful for treating angiogenesis disorder.

The '219 patent teaches that:

Binding of the VEGF dimer to the VEGF receptor is belived to induce receptor dimerization. Dimerization of the receptor then causes autophosphorylation of specific tyrisine residues, Y801, and Y1175, and Y1213, and Y1333 on the intracellular side of VEGFR2 and VEGFR1, respectively. This leads to a signal transduction cascade, which includes activation of phospholipase C*y* and phosphoatidylinosirol 3-kinase, and increase in intracellular calcium ion, see column 45 lines 29-37.

Huang *et al.* provide one of ordinary skill in the art to identify compounds that interfere with or enhance the angiogenesis pathway as they teach that the tight controls on vascular growth in adult tissues can be breached in pathologic states such as cancer, arthritis, and diabetic retinopathy, see page 38183, right column, first paragraph. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to use any of the *in vitro* or *in vivo* assays to determine the interaction between the HCPTPA and VEGFR2, see the experimental section, to identify modulator of angiogenesis. It should be noted that inhibitors of HCPTPA phosphatase activity and VEGFR2 kinase activity are expected to affect both proteins (claims 1 and 2). It should be noted that phosphorelated VEGFR2 is a substrate for HCPTPA, which is disclosed by Haung *et al.* (claims 6).

Since HCPTPA bind specifically to both VEGFR2 and Tie2 and both are known to be involved in vascular growth in tissues, it would have been further obvious to the ordinary skill in the art to add Tie2 to the assay mixture and examine the effect of modulation of HCPTPA on the activity of both VEGFR2 and Tie2 (claims 8, 9, and 13). Finally, the ordinary skill in the art would have been further motivated by the teaching of '219 to measure the activity of VEGER2 by measuring the cellular calcium concentration, which does not require radioactive tracer in the substrate. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTWTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen M. Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1656